# Update on Thin Melanoma: Outcome of an International Workshop

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# Update on Thin Melanoma: Outcome of an International Workshop

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**Key Words:** thin melanoma, Breslow thickness, mitotic rate, growth phase, regression, angiotropism

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A 1-day Workshop of the International Melanoma Pathology Study Group devoted to "The Pathology of Thin Melanoma" (Table 1) was convened on November 12, 2014 in Zurich, Switzerland at University Hospital Zurich. The goals were a general review of current knowledge on this subject with particular reference to histologic definition and description, nomenclature, differential diagnosis, controversies peculiar to thin melanoma, predictors of outcome, and future directions. The Workshop was organized as interactive focus sessions as follows.

## DIAGNOSIS: WHAT IS THIN MELANOMA?; CRITERIA FOR HISTOLOGIC DIAGNOSIS; DEFINITION OF MINIMAL INVASION; SUBTYPES

### Melanoma Microinvasion

Whether a melanoma is in situ or microinvasive is sometimes difficult or impossible to judge even for experts as illustrated by Workshop cases presented. However, it was the view of most Workshop participants that the presence of only a few invasive melanoma cells, still indicative of the radial (horizontal) growth phase, has no significant prognostic impact and therefore might even be disregarded. In contrast, the importance of recognizing the progression from horizontal to vertical growth phase in melanoma was emphasized and may be indicated by the detection of dermal mitoses or dermal nests of melanoma cells larger than junctional nests.

### Thin Melanoma and Breslow Thickness

Dermatopathologists are increasingly confronted with thin melanocytic lesions, and it is well established that there has been a significant increase in the number of thin melanomas ( < 1.0 mm in thickness) over the past 2 to 3 decades. Recent studies indicate that approximately 70% of melanomas are classified as thin. A number of explanations for the latter trends have been suggested, such as causative factors, for example, increased sun exposure, more rigorous reporting of melanoma to cancer registries, "diagnostic drift," and more intensive cancer screening and greater rates of biopsy sampling of pigmented skin lesions.[1] There is continued controversy in the literature about these issues. However, one of the best documented explanations may potentially be attributed to increased skin cancer awareness and skin cancer screening in many western countries. As a result, there is mounting evidence that melanocytic lesions are increasingly being sampled or removed at an early

**TABLE 1.** What Is Thin Melanoma?

| |
|---|
| An expression of epidermal and superficial dermal involvement: |
| "Superficial vs. deep" melanoma |
| An expression of evolution in time: |
| Early melanoma (mélanome débutant) vs. older melanoma |
| An expression of Breslow thickness: |
| < 0.76 mm |
| < 0.85 mm |
| ≤1.0 mm |
| < 1.5 mm |
| An expression of growth phase: |
| Radial or horizontal growth |
| Vertical growth |
| An expression of anatomic level (Clark): |
| Level II (microinvasive) |
| Level III |
| Level IV |

**TABLE 2.** Differential Diagnosis

| |
|---|
| Principal diagnostic problems |
| Melanoma vs. dysplastic nevus |
| Nevoid lentigo maligna vs. dysplastic nevus |
| Nevoid melanoma vs. nevus |
| Nested nevoid melanoma vs. nevus |
| Melanoma vs. pagetoid proliferations |
| Melanoma vs. traumatized nevus |
| Melanoma vs. fibrosing nevus |
| Halo melanoma vs. halo nevus |
| Melanoma vs. spitzoid and pigmented spindle cell lesions |
| Melanoma vs. site-specific nevi |

stage.[2–5] As the cure rate for most thin lesions is excellent, it is likely that these otherwise salutary trends have contributed to the phenomenon of "overdiagnosis" of cancer that is characterized by a rising incidence without a corresponding increase in mortality.[6] Strict criteria for diagnosis of malignancy should be applied, and the evidence suggests that present criteria lack the necessary specificity to reliably discriminate between early melanomas and their simulants (see next section) (Table 1).

## DIFFERENTIAL DIAGNOSIS

### Principal Diagnostic Difficulties

Thin melanomas are often difficult to distinguish from dysplastic nevi, irritated/traumatized melanocytic nevi, inflamed or halo nevi or partially regressed nevi, site-specific nevi (nevi from special anatomic sites), plaque-type Spitz tumors, and pigmented spindle cell nevi. In analogy to macroscopy and the ABCDE rule, we have histologic signs of malignancy (Table 2). In thin melanocytic lesions intratumoral cell heterogeneity with atypical lentiginous melanocytic proliferation and small and large nests of different atypical melanocytes suggest malignancy (Figs. 1A, B). However, for final diagnosis it is crucial to consider all histologic aspects (lesional diameter, eg, banal nevi usually < 5 mm vs. larger size in melanoma), symmetry, lateral demarcation, pagetoid proliferation, degree of cytologic atypia, mitoses, maturation, focal/diffuse host response). For example, pagetoid scatter is not an explicit sign of malignancy, as it can be observed in a variety of melanocytic neoplasms including acral nevi, congenital nevi, nevi in pediatric populations, traumatized nevi, pagetoid Spitz nevi, and pigmented spindle cell nevi.[7] Quite often we observe pagetoid infiltration in dysplastic nevi and are unable to judge whether this means melanoma in situ developing in dysplastic nevus or just irritation of a dysplastic nevus (Figs. 1C, D). However, because of uncertainty in many lesions, the treatment is often the same with excision of about 5 mm margins.

The histologic diagnosis of melanocytic lesions is not standardized. In addition, the consensus for difficult melanocytic lesions is poor even among experts. Interestingly, general agreement on the type of surgical therapy indicated is much better. Consequently, the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) has been proposed. In analogy to BI-RADS (Breast Imaging Reporting and Data System) used in breast imaging, MPATH-Dx facilitates categorization of lesions with diverse nomenclature into a hierarchy of standardized management interventions.[8]

Melanomas on acral skin are usually different from melanomas developing at other anatomic sites such as the trunk, where one often observes superficial spreading variants of melanomas. Many acral melanomas are not obviously malignant on histologic grounds. Thin acral melanomas often exhibit relatively little atypia, no pagetoid spread, and few or no mitoses. Relatively large acral lesions without nest formation and lentiginous melanocytic proliferation with long coarse dendrites should raise concern about acral melanoma. Correlation with clinical features strongly suggesting obvious acral melanoma facilitates the diagnosis (Figs. 2A, B)

Regression in thin melanomas can be difficult to differentiate from a scar in a nevus after trauma or previous excision. Clinical information about localization and previous surgery is critical for a correct diagnosis. Regressed melanomas are often more easily identified on macroscopic grounds because of asymmetry, variegated color, and lack of sharp demarcation. Good clinico-pathologic correlation can facilitate proper diagnosis of regressed melanoma (Figs. 2C, D).

Classical nevoid melanoma often shows high cell density of small cells with hyperchromatic nuclei and relatively scant cytoplasm. There is usually no maturation with depth and mitoses are present by definition. Junctional atypical melanocytic proliferation is usually scanty. Apart from this classical nevoid type, another melanoma shows superficial features of superficial spreading melanoma-type melanoma, which in the superficial to mid dermis change to cells with round hyperchromatic nuclei giving an impression of maturation. The deeper cells are still distinct from benign nevus cells but the suggestion of maturation may lead to misdiagnosis as a benign lesion. For this phenomenon the term pseudo-maturation or paradoxical maturation is used[9,10] (Figs. 2E, F). Preliminary results suggest that this type of nevoid melanoma has a more favorable prognosis versus that of classical nevoid melanoma.

### Gene Expression Analysis for the Distinction of Nevi From Melanoma

Gene expression analysis by quantitative reverse transcriptase polymerase chain reaction was presented to differentiate benign nevi from melanoma. The genes include PRAME (for *p*referentially *e*xpressed *a*ntigen in *m*elanoma); a group of 5 multifunctional genes including S100A7, S100A8, S100A9, S100A12, and PI3; a group of 8

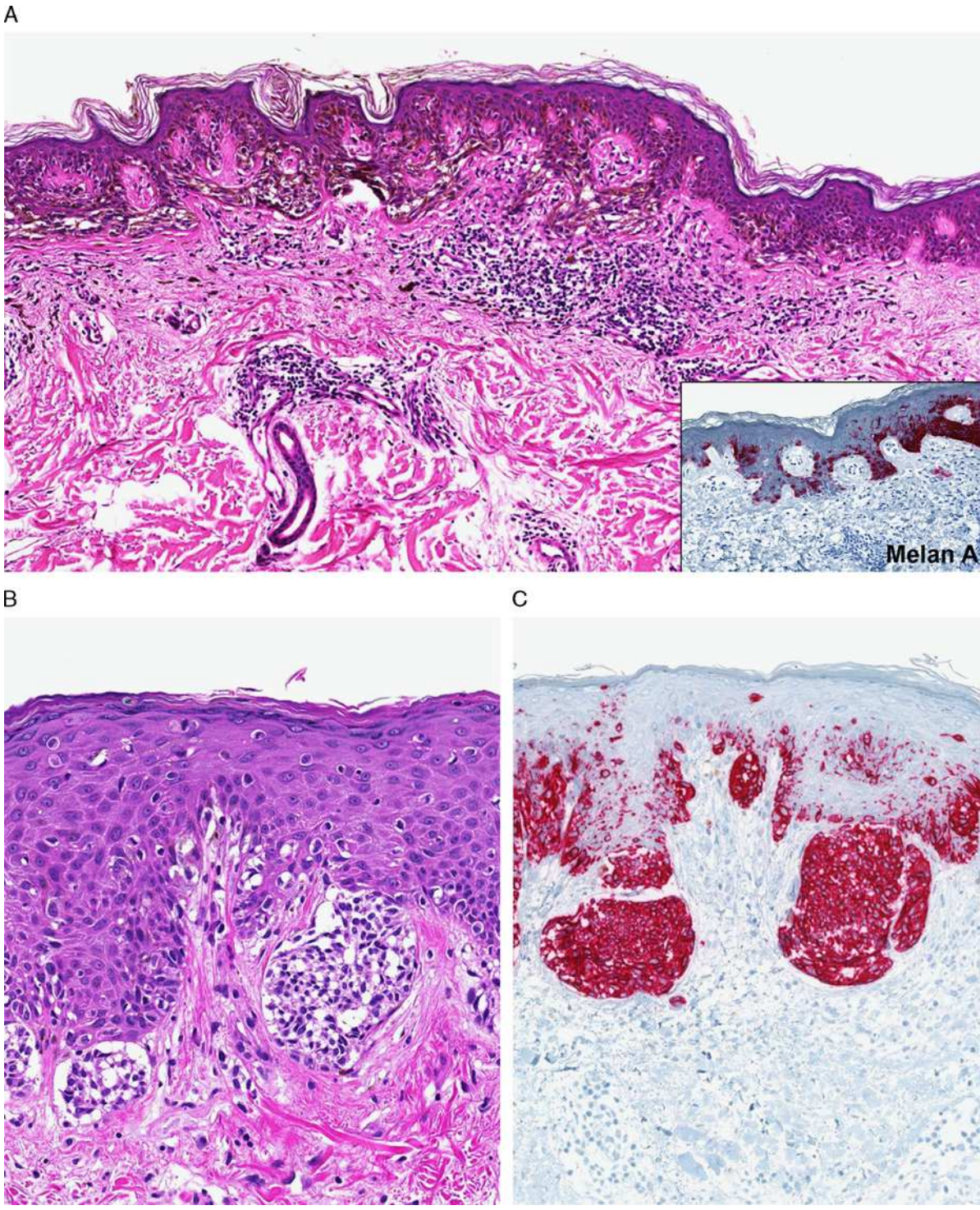


**FIGURE 1.** A–C, A 40-year-old man with SSM-type melanoma on the back. Overview (A) and higher magnification (B, C) illustrating melanoma tumor heterogeneity with atypical lentiginous single cell proliferation, small and large nests of atypical melanocytes (A: HE, ×40; inset: Melan A immunohistochemistry, ×40. B: HE, ×80. C: Melan A immunohistochemistry, ×80). HE indicates hematoxylin and eosin; SSM, superficial spreading melanoma.

genes involved in tumor immune response signaling (*IRF1*, *CCL5*, *CXCL9*, *CXCL10*, *CD38*, *LCP2*, *PTPRC*, *SELL*); and 9 housekeeper genes used for normalization of the expression data (*CLTC*, *MRFAPI*, *PPP2CA*, *PSMA1*, *RPL13A*, *RPL8*, *RPS29*, *SLC25A3*, *TXNLI*). On the basis of analysis of thousands of benign nevi and melanomas a scoring system was developed. Most unequivocally benign nevi have a score $< -2$ and most obvious malignant



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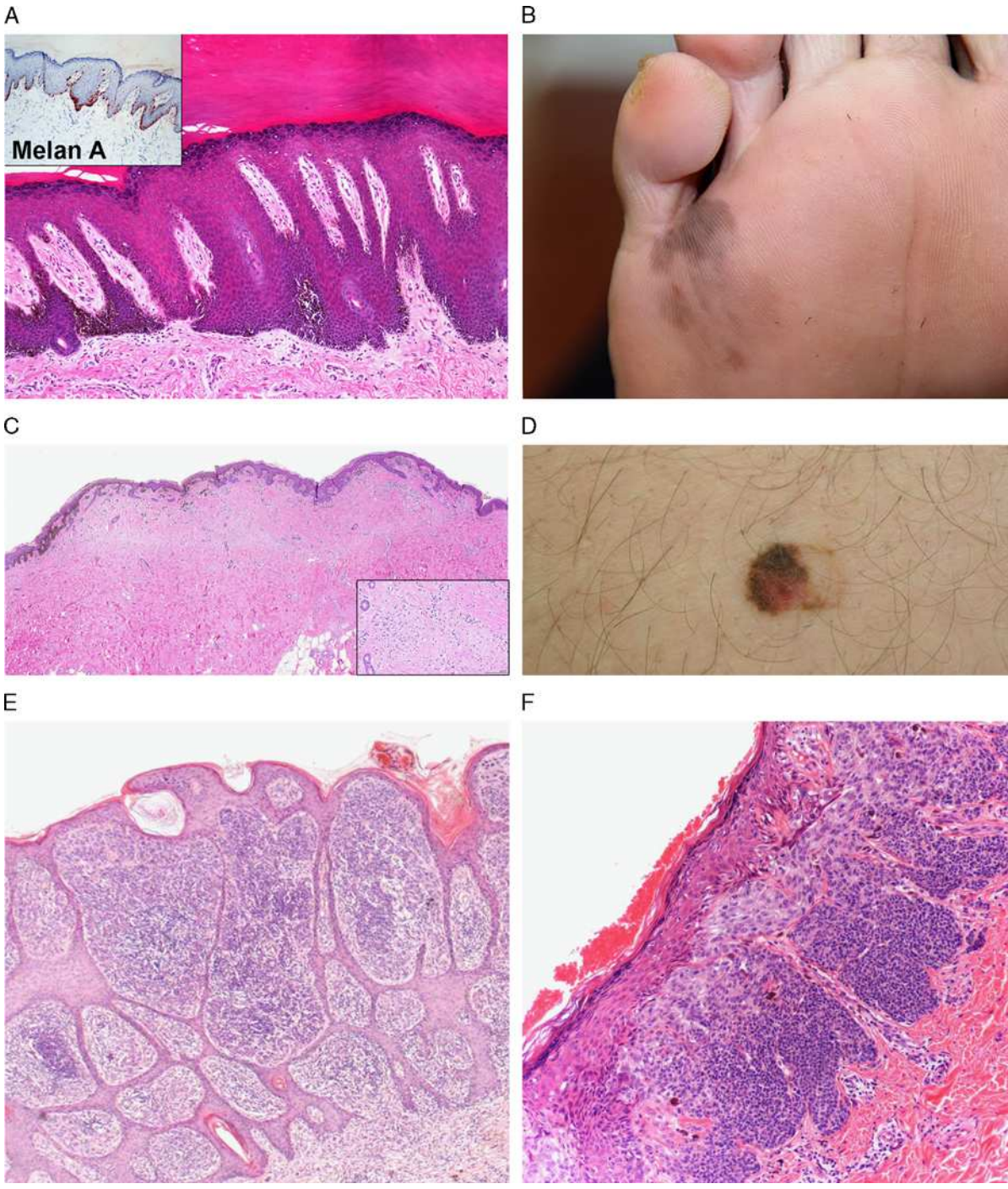


**FIGURE 2.** A and B, A 63-year-old man with acral melanoma right foot. A, Lentiginous melanocytic proliferation, without significant atypia, pagetoid spread, or mitoses. A, HE ×200; inset: Melan A immunohistochemistry, ×200. B, Clinically clear-cut melanoma. C and D, Melanoma with regression in the left lateral thigh. C, Histology with central dermal nevoid component, general symmetry, and features suggesting a benign lesion (HE ×40; inset: HE ×250). D, Clinically the lesion is clear-cut melanoma. E, Classical nevoid melanoma (HE ×50). F, Melanoma with superficial features of SSM-type and deeper small atypical cells suggesting maturation, or so called pseudo-maturation or paradoxical maturation (HE ×200). HE indicates hematoxylin and eosin; SSM, superficial spreading melanoma.

melanoma a score $>0$.[11] However, cases were also described that were not malignant on histologic grounds but the scoring system indicated a malignant lesion. It is crucial to mention that the above-mentioned test includes genes that are normally expressed in benign and malignant melanocytic lesions. Neither specific melanocytic genes nor genes with prognostic significance were represented in the analysis.

**TABLE 3.** Mitotic Activity in Thin Melanoma

| |
|---|
| Breslow thickness, ulceration, and mitotic rate are interrelated |
| In particular, mitotic rate is closely associated with thickness and ulceration |
| Mitotic rates are difficult to assess in thin melanomas, as tissue is limited |
| Greater sampling of tissue aides in the analysis of mitoses |
| There is greater uncertainty about mitoses in thin melanoma |
| Assessment and reproducibility of mitotic rate in thin melanoma have not been sufficiently studied |
| The use of the "hot spot" technique introduces bias, as hot spots are uncommon |
| The mitotic index expressed as mitoses per $mm^2$ may represent the best prognostic value |

## SPECIFIC PROBLEMS IN THIN MELANOMA: MITOTIC ACTIVITY, AJCC/UICC GUIDELINES, etc.

### Thin Melanoma and Mitotic Activity

The prognostic value of mitotic activity in melanoma is well established. However, the inclusion of mitotic rate in the microstaging criteria for thin melanoma in the seventh edition of AJCC and eighth edition UICC classification, respectively, has proved to be controversial (Table 3). Because of the difficulty and uncertainty surrounding assessment of mitotic activity in thin melanomas, many have called for a re-examination of this issue in the microstaging of thin melanoma. Recent NCCN guidelines in the United States recommend that "multiple mitoses" or other risk factors such as ulceration or lymphovascular invasion should be present in melanomas thinner than Breslow's original cutoff of 0.76 mm for low risk, when considering a recommendation for sentinel node staging.[12] It is imperative that accurate and reliable methodology for identification and quantification of mitotic rate is developed. Recent studies have evaluated appropriate tissue sampling and step sectioning to optimize diagnosis of mitotic activity. According to the study results, there is a need for 3 to 5 sections to identify hot spots thereby increasing accuracy of mitotic rate interpretation. Furthermore, there is a general increase in likelihood of finding mitotically active thin melanoma with increasing Breslow depth.[13]

## SPECIFIC PROBLEMS IN THIN MELANOMA: REGRESSION, LYMPHATIC INVASION, AND ANGIOTROPISM

### Regression in thin Melanoma

Regression, usually affecting the radial growth phase, is common in melanoma, particularly in thin lesions. Its incidence among all melanoma tumor thicknesses has been estimated at about 10% to 35% and up to 58% in melanomas with thicknesses $< 0.75$ mm (Table 4). Extensive regression ($> 77\%$ of the tumor) is associated with an adverse clinical outcome.[14] Interestingly, also radial growth phase regression is an adverse prognostic factor. In contrast, tumor-infiltrating lymphocytes representing an active immune response may represent a form of vertical growth phase regression and are associated with a good prognosis.[15–17] These seemingly conflicting observations may be at least partly explained by increased vessel density, especially increased lymphatic vessel density, in areas of regression. Furthermore lymphatic invasion by melanoma may be detected in zones of regression. Increased vessel density as well as lymphatic invasion by melanoma in areas of complete regression are associated with poor clinical outcome.[15,17] However, other studies have not confirmed the latter observations.

**TABLE 4.** Regression in Thin Melanoma

| |
|---|
| Regression is frequent in thin melanoma |
| Focal regression is most common |
| Criteria and reproducibility of recognizing regression remain subjective |

### Angiotropism and Melanoma

The propensity for melanoma to migrate along anatomic structures such as nerves and skin appendages is a common phenomenon. Barnhill and Lugassy's experiments have shown several years ago that melanoma cells migrate along the external surfaces of vascular channels, without intravasation.[18,19] Their revolutionary new paradigm of tumor spread is called extravascular migratory metastases. Recently, in a mouse model, experiments have shown that ultraviolet radiation induces increased rates of angiotropism of melanoma cells, extravascular migration of tumor cells, and an increased frequency of metastasis. In thick melanoma angiotropism is correlated with metastatic disease.[20] The relevance of angiotropism in thin melanomas requires additional study.

## PREDICTORS OF OUTCOME: PROGNOSTIC FACTORS IN THIN MELANOMA

Despite greater and greater molecular characterization of melanoma, Breslow thickness is still among the most powerful prognostic factors in both the AJCC and UICC schemes (Table 5).[21,22] Thin melanomas are classified as pT1 stage with tumor thickness $< 1$ mm. Despite the excellent prognosis of thin melanomas, 20% are associated with metastasis and 5% are fatal.[23] As a consequence of increasing numbers of thin melanoma, these facts cannot any longer be neglected. There is a need to identify this subgroup with adverse clinical outcome. Breslow's original publication showed that all patients with tumor thickness $< 0.76$ mm were disease free at 5 years. Nonetheless, Breslow acknowledged that undoubtedly rare melanomas $< 0.76$ mm with adverse outcome exist. For practical purposes, thereafter, a threshold of 1 mm was chosen to define thin melanoma. Recent studies confirm Breslow's findings

**TABLE 5.** Prognostic Factors in Thin Melanoma

| |
|---|
| Breslow thickness: |
| $< 0.76$ mm—very low risk |
| $> 0.76$ mm—greater risk |
| Growth phase |
| Clark level |
| Mitotic rate |
| Ulceration |
| Regression |
| Lymphatic invasion |
| Angiotropism of melanoma cells—requires further study in this thickness category |



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that almost all thin melanomas that develop metastases show a tumor thickness between 0.75 and 1 mm.[24] Therefore, we recommend that an upper limit of 0.75 mm should be considered for thin melanomas.

Combinations of adverse risk factors can subdivide the low-risk stage I group as currently defined. Gimotty et al[25] used Breslow thickness with a cutoff of 0.78 mm, with various combinations of Clark level, sex, age, site, and mitogenicity to identify subgroups with 10-year survival probabilities ranging from 83% to 99%.

Clark level is no longer required for TNM staging and accordingly is no longer mentioned in many melanoma reports. However, it should be emphasized that especially in thin melanoma Clark level has prognostic significance and should be reported.[24,26]

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